IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	))))	C.A. No. 05-356-KAJ (consolidated)

NOTICE OF DEPOSITION UNDER FED. R. CIV. P. 30(b)(6)
TO ALPHAPHARM PTY LTD.

PLEASE TAKE NOTICE that on April 27, 2006 commencing at 9:00 a.m., at the offices of Covington & Burling, 1201 Pennsylvania Avenue, N.W., Washington, D.C. 20004, Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P. and Synaptech, Inc. (collectively, "Plaintiffs" or "Janssen") will take the deposition upon oral examination of Defendant Alphapharm Pty Ltd. ("Alphapharm") pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure. This deposition upon oral examination will be conducted before an officer authorized to administer oaths and will be recorded by stenographic and videographic means.

Plaintiffs serve this Notice without waiver of its objections to the deficiencies in Alphapharm's document production and other discovery responses concerning the subject matter of the instant Notice, and reserve the right to continue this deposition as necessary in light of any subsequent document production by Alphapharm.

Plaintiffs will take this deposition upon oral examination through one or more officers, directors, managing agents or other persons designated by Alphapharm pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure as the person(s) knowledgeable to testify on Alphapharm's behalf concerning the topics identified in Schedule A. Alphapharm is requested to provide counsel for Plaintiffs with the identity of the individual(s) who will testify regarding each topic at least one week in advance of the deposition. The deposition

will continue from day to day until completed with such adjournments as to time and place as may be necessary. You are invited to attend and examine the witness(es).

ASHBY & GEDDES

/s/ Lauren E. Maguire

Steven J. Balick (I.D. #2114)
John G. Day (I.D. #2403)
Tiffany Geyer Lydon (I.D. #3950)
Lauren E. Maguire (I.D. #4261)
222 Delaware Avenue, 17th Floor
P.O. Box 1150
Wilmington, DE 19899
(302) 654-1888

Attorneys for Janssen Pharmaceutica N.V., Janssen, L.P., and Synaptech, Inc.

Of Counsel:

George F. Pappas
Roderick R. McKelvie
Christopher N. Sipes
Jeffrey B. Elikan
Laura H. McNeill
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004
Tel: 202-662-6000
Fax: 202-662-6291

Steven P. Berman
Office of General Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Tel: 732-524-2805
Fax: 732-524-5866

Dated: February 21, 2006
166721.1

SCHEDULE A

Definitions

1. As used herein, "Alphapharm" shall mean Defendant Alphapharm Pty Ltd. and all of Alphapharm Pty Ltd.'s corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees.

2. As used herein, "Alphapharm's ANDA" shall mean Alphapharm's Abbreviated New Drug Application Number 77-603.

3. As used herein, "the Generic Product" shall mean the proposed generic galantamine product that is the subject of Alphapharm's ANDA.

4. As used herein, "the '318 patent" shall mean United States Patent No. 4,663,318.

5. As used herein, "document" shall have the full meaning ascribed to it by the Federal Rules of Civil Procedure and shall include any means for retaining information.

6. As used herein, "FDA" shall mean the United States Food and Drug Administration.

7. As used herein, "Paragraph IV notice" refers to Alphapharm's May 11, 2005 letter to Plaintiffs attached hereto as Exhibit 1.

8. "Person" and "persons" mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

9. "Alzheimer's Disease" means any diagnosis, illness, or ailment described as being of the Alzheimer's type, including without limitation Senile Dementia of the Alzheimer's Type, and/or Alzheimer's Dementia.

10. "Galantamine" includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

Topics of Examination

1. Alphapharm's Paragraph IV notice including, without limitation, the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "the '318 patent … [is] invalid."

2. Any evaluation, consideration or discussion conducted by Alphapharm to develop the Generic Product, including the names and responsibilities of all persons who were involved in the evaluation, consideration or discussion by Alphapharm to develop the Generic Product.

3. The decision to file an application with the FDA seeking approval to manufacture and sell a drug product containing galantamine.

4. Any evaluation, consideration or discussion conducted by Alphapharm to market the Generic Product, including the names and responsibilities of all persons who were involved in the evaluation, consideration or discussion by Alphapharm to market the Generic Product.

5. The benefits, including revenues and profits, that Alphapharm projects, anticipates, expects, or forecasts it will obtain should Alphapharm's ANDA receive approval from the U.S. Food and Drug Administration.

6. Marketing strategies, marketing plans, and projected sales for Alphapharm's Generic Product.

7. Each and every contribution and/or input that Alphapharm, or any employee or agent of Alphapharm, has made to the preparation, decision to file, filing and/or prosecution of Alphapharm's ANDA, including: (a) any information relating to regulatory procedures and strategies for obtaining regulatory approval of the Generic Product of

Alphapharm's ANDA; (b) any information comprising, relating to or contained in the 21 U.S.C. § 355(j)(2)(A)(vii)(IV) certifications submitted in connection with Alphapharm's ANDA; and (c) any information comprising, relating to or contained in the statements of factual and legal basis for invalidity, unenforceability, and/or noninfringement included with the notice of these certifications.

8. The factual basis for Alphapharm's proposed assertion that Alphapharm's ANDA is indicated for the treatment of mild to moderate Alzheimer's disease.

9. The circumstances in which Alphapharm first became aware of galantamine as a treatment for Alzheimer's disease, including but not limited to the date on which this occurred and the people involved.

10. The circumstances in which Alphapharm first became aware of the '318 patent, including but not limited to the date on which this occurred and the people involved.

11. Any consideration or evaluation by Alphapharm to develop a drug product containing galantamine for the treatment of Alzheimer's Disease.

12. Identification of all individuals, whether employees of Alphapharm or third parties, having a role in the consideration or evaluation by Alphapharm to develop a drug product containing galantamine for the treatment of Alzheimer's disease that is the subject of Topic 11, and a description of those roles.

13. Any effort by Alphapharm to develop any drug product other than the Generic Product set forth in Alphapharm's ANDA.

14. Identification of all individuals, whether employees of Alphapharm or third parties, having a role in the research, development or testing of such a treatment responsive to Topic 13, and a description of those roles.

15. The factual and legal bases for Alphapharm's Second Affirmative Defense that each claim of the '318 patent is invalid for failure to satisfy one or more of sections 101, 102, 103, 112 and 116 of Title 35 of the United States Code.

16. The factual and legal bases for Alphapharm's Second Counterclaim that each claim of the '318 patent is invalid for failure to satisfy one or more of sections 101, 102, 103, 112 and 116 of Title 35 of the United States Code according to its proof elements, including an element-by-element comparison of each asserted claim of the '318 patent to the prior art Alphapharm relies upon and the motivation of one of skill in the art to combine any references under 35 U.S.C. §103, as well as a description of any non-prior art defenses such as lack of enablement, insufficient written description, failure to disclose best mode, or claim indefiniteness under 35 U.S.C. § 112.

17. The identity and location of documents and things concerning the foregoing topics.

18. Alphapharm's document retention policies from 1986 to the present.

19. Persons knowledgeable about the subject matter of the foregoing topics.

166721.1

EXHIBIT 1

WCW
MAY 1 2 2005

CONFIDENTIAL

May 11, 2005

alphapharm

VIA (1) REGISTERED MAIL
RETURN RECEIPT REQUESTED and
(2) FEDERAL EXPRESS

P.K. Miller
President
Janssen Pharmaceutica Products, L.P.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

William C. Weldon
Chairman and Chief Executive Officer
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

Ajit Shetty
President
Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse, Belgium

Janssen Pharmaceutica N.V.
c/o U.S. Correspondent
Audley A. Ciamporcero, Jr.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

President and Chief Executive Officer
Synaptech Inc.
c/o Schwartz & Salomon
225 Broadway – 42nd Floor
New York, NY 10007

Synaptech Inc.
c/o Correspondent John Richards
Ladas & Perry
26 West 61st Street
New York, NY 10023

Re: Galantamine Hydrobromide Tablets, 4 mg, 8 mg and 12 mg
U.S. Patent Nos. 4,663,318; 6,099,863 and 6,358,527:
Notice of Paragraph IV Certifications

Dear Sir:

This is a notice-of-certification letter on behalf of Alphapharm Pty Ltd. ("Alphapharm") pursuant to § 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act ("the Act") and § 314.95 of Title 21 of the Code of Federal Regulations:

1. In order to obtain approval to engage in the commercial manufacture, use or sale of Galantamine Hydrobromide Tablets 4 mg, 8 mg and 12 mg, Alphapharm submitted to the Food and Drug Administration ("FDA") an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Act that contains any required bioavailability or bioequivalence data or information.

2. The ANDA number is 77-603 ("Alphapharm's ANDA").

Alphapharm Pty Limited
ABN 93 002 359 739
PO Box 36 Carlingford NSW 1450

Head Office Chase Building 2
Wentworth Park Road Glebe NSW 2037
T 02 9298 3999 F 02 9566 4686

Manufacturing / Research & Development
15 Garnet Street Carole Park QLD 4300
T 07 3000 4400 F 07 3000 8565

Customer Service
T 1800 977 421 F 1800 358 193
www.alphapharm.com.au

3. The established name of the proposed drug product is galantamine hydrobromide tablets. Janssen Pharmaceutica Products, L.P. ("Janssen"), markets galantamine hydrobromide tablets, 4 mg, 8 mg, and 12 mg and oral solution (4mg/ml), under the brand name REMINYL®.

4. The active ingredient, strength and dosage form of the proposed drug product are galantamine hydrobromide 4 mg, 8 mg and 12 mg tablets ("Alphapharm's tablets").

5. The ANDA indicates that the Applicant intends to market the product before the expiration of United States Patent No. 4,663,318 ("the '318 patent"), which expires on December 14, 2008. The '318 patent is listed in *Approved Drug Products With Therapeutic Equivalence Evaluations* ("the Orange Book") for galantamine 4 mg, 8 mg and 12 mg tablets.

6. The ANDA indicates that the Applicant intends to market the product before the expiration of United States Patent No. 6,099,863 ("the '863 patent"), which expires on June 6, 2017. The '863 patent is listed in the Orange Book for galantamine 4 mg, 8 mg and 12 mg tablets.

7. The ANDA indicates that the Applicant intends to market the product before the expiration of United States Patent No. 6,358,527 ("the '527 patent"), which expires on June 6, 2017. The '527 patent is listed in the Orange Book for galantamine 4 mg, 8 mg and 12 mg tablets.

8. Alphapharm's ANDA indicates that in Alphapharm's opinion and to the best of its knowledge, the '318, '863 and '527 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Alphapharm's galantamine hydrobromide tablets that are the subject of Alphapharm's ANDA.

9. An offer of Confidential Access to Alphapharm's ANDA 77-603, pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Attached is a detailed statement of the factual and legal bases of Alphapharm's paragraph IV patent certifications regarding the '318, '863 and '527 patents. This information is supplied for the sole purpose of complying with the above-referenced statute and regulations. Neither Alphapharm nor its attorneys waive any attorney-client privilege or work-product immunity concerning the subject matter of this communication.

Sincerely,

Dr. Brett Mooney
Alphapharm Pty. Ltd.
15 Garnet Street
Carole Park
QLD 4300
Brisbane AUSTRALIA

U.S. Correspondent:

Christina Markus
King and Spaulding
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006-4706
USA

Enclosure: Detailed Statement of the Factual and Legal Bases of Alphapharm's Paragraph IV Patent Certification Regarding U.S. Patent Nos. 4,663,318, 6,099,863 and 6,358,527.

Offer of Confidential Access to Alphapharm's ANDA

DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES FOR ALPHAPHARM'S OPINION THAT UNITED STATES PATENT NOS. 4,663,318, 6,099,863 AND 6,358,527 ARE INVALID, UNENFORCEABLE AND/OR WILL NOT BE INFRINGED

I. INTRODUCTION AND SUMMARY OF ARGUMENTS

Prior to the filing of the patents in suit, anticholinesterase inhibitors, including physostigmine and tacrine, were used to treat Alzheimer's disease. The art recommended that other anticholinesterase inhibitors be tested for use in treating Alzheimer's disease and galantamine[1] was a known anticholinesterase inhibitor that had been used therapeutically and was known to cross the blood brain barrier.

In 1986, Bonnie Davis filed the patent application that led to the '318 patent, which claims methods of using galantamine tablets to threat Alzheimer's disease. The application comprises slightly more than a one page specification and a quarter page of claims. The application hypothesizes that galantamine tablets may be used to treat Alzheimer's disease but does not set forth any completed tests or experiments.

About ten years after Davis filed her method patent, Janssen Pharmaceutica N.V. filed the applications that eventually led to the '863 and '527 U.S. patents. The '863 patent narrowly claims a galanthamine hydrobromide tablet formulation with specific ratios of particular diluent components. The '527 patent claims a tablet and methods of treating various disorders, including Alzheimer's disease by administering a tablet formulation having the same specific ratio of the particular diluent components as the '863 patent.

Janssen filed NDA 21-224 and obtained approval to market its galantamine hydrobromide tablets under the brand name REMINYL® in June 2001. Janssen listed the '318, '863 and '527 patents in the Orange Book.

Alphapharm's 4 mg, 8 mg and 12 mg galantamine hydrobromide tablets do not infringe any valid claims of the '318, '863 or '527 patents. Alphapharm's tablets do not use the specific ratio of diluent components claimed in the '863 or '527 patents and thus do not infringe either of these patent. Alphapharm's tablets claims will not meet the claimed dosage ranges or administration routes of claims 2, 3, 5, 6 or 7 of the '318 patent and thus, will not infringe these claims. The '318 patent is also invalid over prior art.

[1] Galantamine is also known as Galanthamine. Both terms are used interchangeably throughout this letter.

II. ALPHAPHARM'S PROPOSED ANDA PRODUCT

Alphapharm proposes to manufacture, as set forth in its ANDA specification, galantamine hydrobromide 4 mg, 8 mg and 12 mg tablets. Alphapharm's proposed 4 mg galantamine hydrobromide tablets contain:

- 5.128 mg of galantamine hydrobromide (equivalent to 4 mg galantamine)
- 48.272 mg of lactose monohydrate (spray-dried)
- 5 mg of crospovidone
- 1 mg of silica colloidal anhydrous
- 0.6 mg of magnesium stearate
- 1.8 mg of opadry white OY-LS-28908

Alphapharm's proposed 8 mg galantamine hydrobromide tablets contain twice the amount of each ingredient in Alphapharm's proposed 4 mg galantamine hydrobromide tablets. Alphapharm's proposed 12 mg galantamine hydrobromide tablets contain three times the amount of each ingredient in Alphapharm's proposed 4 mg galantamine hydrobromide tablets.

In Alphapharm's proposed product, lactose monohydrate is the sole diluent used in the formulation.

III. LEGAL STANDARDS FOR INFRINGEMENT AND INVALIDITY

A. Infringement Generally

35 U.S.C. § 271(e)(2) provides in pertinent part that "[i]t shall be an act of infringement to submit—(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent."

"35 U.S.C. § 271(e)(2) provides an 'artificial' act of infringement that creates case–or–controversy jurisdiction to enable the resolution of an infringement dispute before the ANDA applicant has actually made or marketed the product. Once jurisdiction is established, however, the substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis...." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

The patentee has the burden of proving infringement by a preponderance of the evidence. *Amstar Corp. v. Envirotech Corp.*, 823 F.2d 1538, 1545 (Fed. Cir. 1987). Infringement may be literal or under the doctrine of equivalents. In each case the infringement analysis is a two-step process. First, the scope of the claims must be determined. The Supreme Court has held that this first step, sometimes referred to as claim interpretation, is an issue of law exclusively within the province of the court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) ("*Markman II*"); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1453 (Fed. Cir. 1998) (en banc). Thus, claim construction necessarily precedes a determination of whether the claims read on an accused product (or

process) for infringement purposes. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990), *cert. dismissed*, 499 U.S. 955 (1991); *SmithKline Diagnostics, Inc. v. Helena Labs Corp.*, 859 F.2d 878, 882 (Fed. Cir. 1988).

The second step involves comparing the properly construed claims to the accused product or process to determine whether those claims "read on" the accused subject matter, i.e., whether all of the claim limitations are present in the accused device, either literally or by a substantial equivalent. *Johnson Worldwide Assocs. Inc. v. Zebco Corp.*, 175 F.3d 985, 988 (Fed. Cir. 1999); *Renishaw PLC v. Marposs Societa per Azioni*, 158 F.3d 1243, 1247 (Fed. Cir. 1998); *Cybor*, 138 F.3d at 1453; *Read Corp. v. Portec Inc.*, 970 F.2d 816, 821-22 (Fed. Cir. 1992) (aff'd in part, rev'd in part on other grounds). This second step is a factual determination and is thus submitted to a jury if the case is not tried to the court. *Markman II*, 517 U.S. at 385 (citing *Winans v. Denmead*, 56 U.S. 330, 15 How. 330, 338 [1854]).

1. Claim Interpretation

Claim interpretation involves consideration of the language of the patent claim itself, the specification, other claims, the prosecution history, and extrinsic evidence, if necessary. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) *aff'd en banc*, 517 U.S. 370 (1996) ("*Markman I*"); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Extrinsic evidence is any evidence which is external to the patent and prosecution history, such as expert testimony, inventor testimony, dictionaries, and technical treatises and articles. *Vitronics*, 90 F.3d at 1584. Finally, "the claims of [a] patent cannot be given a construction broader than the teachings expressed in the patent." *Studiengesellschaft Kohle GmbH v. Eastman Kodak, Inc.*, 616 F.2d 1315, 1324 (5th Cir.), *cert. denied*, 449 U.S. 1014 (1980). Thus, the scope of the claims can be no broader than the scope of the novel invention taught by the patentee in the specification.

The specification should be referred to when construing the limitations of patent claims. Indeed, usually, it is dispositive of the meaning of a term, and has been called "the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582. Thus, the specification may act as a sort of dictionary, which explains the claimed subject matter and may define terms used in the claims. *Markman I*, 52 F.3d at 979; *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1153 (Fed. Cir.), *reh'g denied*, 120 F.3d 1260 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 1109 (1998). Where the specification contains nothing to indicate that phrases are to be given anything other than their ordinary meanings, then those are the meanings the court must give them. *Enercon GmbH v. Int'l Trade Comm'n*, 151 F.3d 1376, 1384 (Fed. Cir. 1998) (citing *Vitronics*, 90 F.3d at 1582); *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 759 (Fed. Cir. 1984). Thus, a technical term used in a patent document is given the same meaning that it would be given by persons experienced in the field of the patent, unless it is apparent from the patent and prosecution history that the patentee used the term with a different meaning. *CVI/Beta Ventures*, 112 F.3d at 1153, citing *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996) ("it is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning").

2. Literal Infringement

After claim interpretation, a determination is made whether the claims cover the accused products or methods. *Johnson Worldwide Assocs.*, 175 F.3d at 988. In order to infringe a claim, the accused product or method must include every limitation of the claim, either literally or by a substantial equivalent. *Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397 (Fed. Cir. 1994).

To demonstrate literal infringement, a plaintiff must prove that the allegedly infringing product or method embodies every element of the asserted claim(s). *Dolly, Inc.*, 16 F.3d at 397; *Townsend Eng'g Co. v. Hitec Co.*, 829 F.2d 1086, 1090 (Fed. Cir. 1987). This follows from the principle that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention." *Lemelson v. United States*, 752 F.2d 1538, 1551 (Fed. Cir. 1985) (it is well settled that each element of a claim is material and essential). Thus, "[i]f even one limitation is missing or not met as claimed, there is no literal infringement." *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).

3. The Doctrine of Equivalents

Even if a product or process does not literally infringe, there can still be infringement if there is "equivalence" between the elements of the accused product or process and the elements of the patent's claims. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605 (1950); *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997); *We Care, Inc. v. Ultra-Mark Int'l Corp.*, 930 F.2d 1567, 1571 n.3 (Fed. Cir. 1991). Infringement by equivalents requires that "the accused product or process contain elements identical or equivalent to each claimed element of the patented invention." *Warner-Jenkinson*, 520 U.S. at 40.

To be equivalent, the patentee must prove that the accused product "differs from what is literally claimed only insubstantially, and it performs substantially the same function in substantially the same way to achieve substantially the same result." *Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1444 (Fed. Cir. 1997); *see Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1518 (Fed. Cir. 1995), *rev'd on other grounds*, 520 U.S. 17 (1997) (affirming the viability of the "insubstantial differences" test); *Texas Instruments, Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567 (Fed. Cir. 1996). The nature of the differences is assessed according to whether a person with ordinary skill in the relevant art would find the differences to be substantial. *Hilton Davis*, 62 F.3d at 1519.

4. Limits on the Doctrine of Equivalents

There are, of course, limitations on the application of the doctrine of equivalents. Both the prior art and prosecution history estoppel limit the range of equivalents. *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1579 (Fed. Cir. 1993), *clarified on other grounds*, 15 F.3d 1076 (Fed. Cir. 1994); *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 934 n.1 (Fed. Cir. 1987) (en banc).

Prosecution history estoppel applies when the applicant surrenders subject matter by either argument or amendment. Arguments (without amendment) made during prosecution to obtain allowance of the claims at issue give rise to estoppel when such assertions clearly and unmistakably surrender subject matter, even when such arguments were not necessary to secure allowance of the claims. *See Sextant Avionique, S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 828, n.3 (Fed. Cir. 1999) (citing *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 952 (Fed. Cir. 1993)); *Texas Instruments Inc. v. United States Int'l Trade Comm'n*, 988 F.2d 1165, 1174-75 (Fed. Cir. 1993); *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1458 (Fed. Cir. 1998)).

A narrowing amendment made during the prosecution of a patent to satisfy any requirement of the Patent Act may give rise to an estoppel. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 122 S. Ct. 1831, 1839 (2002). For example, prosecution history estoppel is not limited to amendments made to avoid the prior art, but rather includes amendments made to comply with 35 U.S.C. § 112:

> A patentee who narrows a claim as a condition for obtaining a patent disavows his claim to the broader subject matter, whether the amendment was made to avoid the prior art or to comply with § 112. We must regard the patentee as having conceded an inability to claim the broader subject matter or at least as having abandoned his right to appeal a rejection. In either case estoppel may apply.

Id. at 1840. When prosecution history applies, the patentee may only allege literal infringement.

In addition, arguments emphasizing the criticality of a claim element may give rise to a surrender of all competitive products that do not contain the critical element. *See Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1378-79 (Fed. Cir. 1999) (finding all compositions that do not contain a component described as critical during prosecution and interpreted as indispensable were surrendered during prosecution).

Moreover, there can be no infringement under the doctrine of equivalents if a claim limitation is totally missing from the accused device. *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1539 (Fed. Cir. 1991) (quoting *Wahpeton Canvas Co., Inc. v. Frontier Inc.*, 870 F.2d 1546, 1552, n.9 (Fed. Cir. 1989)). "The doctrine of equivalents is not a license to ignore claim limitations." *Dolly*, 16 F.3d at 398. A "court cannot convert a multilimitation claim to one with fewer limitations to support a finding of equivalency." *Id.* at 399.

B. Invalidity: Anticipation Legal Standards

The patent law imposes certain fundamental conditions for patentability, paramount among them being the condition that what is sought to be patented, as determined by the claims, be new. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 780 (Fed. Cir. 1985); 35 U.S.C. § 102.

35 U.S.C. § 102(b), which creates an absolute bar to patentability, states:

> A person shall be entitled to a patent unless—(b) the invention was patented or described in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

To establish anticipation, a party must show identity of invention "either expressly or under principles of inherency, in a single prior art reference, or that the claimed invention was previously known or embodied in a single prior art device or practice." *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1565 (Fed. Cir. 1992). As a matter of law, if the prior art describes a species covered by a claim, the claim is invalid. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

C. Invalidity: Obviousness Legal Standards

For a patent to be valid, the claimed invention must be nonobvious over the prior art to a person of ordinary skill in the art of the invention. 35 U.S.C. § 103(a) provides in part that:

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains....

An important consideration is "the need to adhere to the statute, i.e., to hold that an invention would or would not have been obvious as a whole, when it was made, to a person of 'ordinary skill in the art' – not to the judge, or to a layman, or to those skilled in remote arts, or to geniuses in the art." *Envtl. Designs Ltd., v. Union Oil Co.*, 713 F.2d 693, 697 (Fed. Cir. 1983); *Custom Accessories Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Courts have set forth factors that can guide an assessment of obviousness including the following:

(1) the scope and content of the prior art;

(2) the differences between the prior art and the claims at issue;

(3) the level of the ordinary skill in the art; and

(4) whatever objective evidence may be present.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966).

When evaluating the scope and content of the prior art, the question under § 103 is not merely what the references expressly teach, but what they would have suggested to one of ordinary skill in the art at the time the invention was made. *Merck & Co. Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). To invalidate a patent under § 103 using a combination of prior art, there must be some reason, suggestion or motivation found in the prior art whereby a person of ordinary skill would make the combination. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1351 (Fed. Cir. 1998), *reh'g denied*, 161 F.3d 1380 (Fed. Cir. 1998). The motivation to combine can come from the knowledge of those skilled in the art, from the prior art reference itself, or from the nature of the problem to be solved. *Sibia Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000). The ultimate determination of obviousness when evaluating the prior art does not require absolute predictability of success. All that is required is a reasonable expectation of success. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000).

Other considerations may be helpful in determining whether an invention is obvious. These secondary considerations include evidence of commercial success, long felt but unsolved needs, failure of others, initial skepticism of experts, praise from experts, copying by an infringer, near simultaneous invention by others, licenses under the examined patent, and prior failure of others. *Graham*, 383 U.S. at 17.

D. Invalidity: Written Description, Enablement, and Indefiniteness Legal Standards

The first paragraph of 35 U.S.C. § 112 states that "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . ." In other words, a patent is invalid unless it contains the required enabling description. *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

The enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims. *See Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196-97 (Fed. Cir. 1999). A specification is not enabling when it discourages experimentation or tells the public that it will not work. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244-45 (Fed. Cir. 2003). The scope of the claims must be less than or equal to the scope of enablement in the specification. *See* 166 F.3d at 1196.

The purpose of the definiteness requirement of § 112, second paragraph, is to force patentees to draft claims with clarity and precision. *See Standard Oil Comp. v. Am. Cyanamid Co.*, 775 F.2d 448, 453 (Fed. Cir. 1985); *In re Borkowski*, 422 F.2d 904, 952 (C.C.P.A. 1970). The determination of whether a claim is invalid as indefinite is dependent upon whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification. *See Atmel Corp., v. Info. Storage Devices, Inc.*, 198 F.3d 1374, 1378 (Fed. Cir. 1999); *Charvat v. Comm'r of Patents*, 503 F.2d 138, 149 (D.C. Cir. 1974).

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993) (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986)); *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed. Cir.), *cert. dismissed*, 474 U.S. 976 (1985). The court first examines the intrinsic evidence to determine whether the terms are indefinite. *See Miles*, 997 F.2d at 875; *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed. Cir. 1997). If the intrinsic evidence fails to provide a definite meaning for the term, the court then examines the extrinsic evidence. *See Bell*, 132 F.3d at 706. The Federal Circuit has also recognized that indefiniteness should be considered from the perspective of a potential competitor. *See Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1996).

An otherwise definite claim risks invalidity on the ground of indefiniteness if the patentee asserts a scope for it which differs from the ordinary and natural meaning of the language of the claim. *See Plastic Container Corp. v. Continental Plastics of Oklahoma, Inc.*, 607 F.2d 885, 896 (10th Cir. 1979). A claim that seems definite standing alone can take on an unreasonable degree of uncertainty when read with the specification. *In re Moore*, 439 F.2d 1232, 1235 n.2 (C.C.P.A. 1971). Thus, a claim is indefinite if, after reading the claims and specifications together, one can no longer tell what the invention is because the ordinary meaning of the claim language is inconsistent with the description and examples in the specification. *In re Cohn*, 438 F.2d 989, 993 (C.C.P.A. 1971).

IV. The '863 and '527 Patents Are Not Infringed

A. The '863 Patent Claims and Specification

The '863 patent to Gilis et al. issued on August 8, 2000 and is assigned to Janssen Pharmaceutica N.V. The '863 patent will expire on June 6, 2017.

The '863 patent has 10 claims directed toward a tablet having an effective amount of galantamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, which comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and to a method of preparing the tablet. Only claim 1 is independent:

1. A tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.

2. A tablet according to claim 1 wherein the disintegrant is crospolyvidone or croscarmellose.

3. A tablet according to claim 1 wherein the carrier further comprises a glidant and a lubricant.

4. A tablet according to claim 3 wherein the glidant is colloidal anhydrous silica and wherein the lubricant is magnesium stearate.

5. A tablet according to claim 1 comprising by weight based on the total weight:

(a) from 2 to 10% galanthamine hydrobromide (1:1);

(b) from 83 to 93% spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25);

(c) from 0.1 to 0.4% glidant;

(d) from 3 to 8% insoluble crosslinked polymeric disintegrant; and

(e) from 0.2 to 1% lubricant.

6. A tablet according to claim 5 comprising

(a) about 2 to 10% galanthamine hydrobromide (1:1);

(b) about 83 to 93% spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25);

(c) about 0.2% colloidal anhydrous silica;

(d) about 5% crospolyvidone; and

(e) about 0.5% magnesium stearate.

7. A tablet according to claim 1 which is film-coated.

8. A tablet according to claim 7 wherein the film-coat comprises a film-forming polymer and a plasticizer.

9. A tablet according to claim 8 wherein the film-coat weighs from about 3% to about 8% of the uncoated tablet core.

10. A process of preparing a tablet according to claim 3 comprising the steps of:

(i) dry blending the active ingredient, the disintegrant and the optional glidant with the diluent;

(ii) optionally mixing the lubricant with the mixture obtained in step (i);

(iii) compressing the mixture obtained in step (i) or in step (ii) in the dry state into a tablet; and

(iv) optionally film-coating the tablet obtained in step (iii).

The '863 patent is directed to a fast-dissolving oral tablet with at least 80% dissolution after 30 minutes. (Col. 1, ll. 9-10; col. 2, ll. 60-63). The '863 patent acknowledges prior art galanthamine hydrobromide tablets having lactose monohydrate as a diluent and microcrystalline cellulose as a disintegrant, (col. 1, ln. 66-col. 2, ln. 36; col. 3, ll. 10-14), but notes that the prior art tablets were unable to provide a dissolution of 80% after 30 minutes. According the '863 patent, this dissolution specification is only met by using a "particular diluent containing a disintigrant [sic], and a second disintegrant." (Col. 2, ll. 65-68). The '863 patent explains that to solve the problems of the prior art, the diluent of the prior art was substituted with a spray-dried mixture of lactose monohydrate and microcrystalline cellulose in a 75:25 ratio. (Col. 3, ll. 19-23).

B. The '863 Patent Prosecution History

The '863 patent issued from U.S. Application No. 09/202,187, which was filed on December 9, 1998 as a § 371 National Stage of PCT Application No. PCT/EP97/02986, which was filed on June 6, 1997, and which claims priority to EP 96/201,676, filed June 14, 1996.

Upon entering the U.S. national stage, the applicants filed a preliminary amendment amending improper multiple dependent claims. (Dec. 9, 1998 Prel. Amend.) The Examiner rejected claims 1, 3-5 and 7-10 as not enabled because the specification stated that the disintegrant crospolyvidone or croscarmellose is critical or essential to the practice of the invention, but the disintegrant was not included in the claims. (Oct. 15, 1999 OA, p. 2). In its January 18, 2000 Amendment, applicants amended the claim to recite an "insoluble or poorly soluble cross-linked polymer disintegrant", which "provides the required dissolution specification of 80% after 30 minutes." (Jan. 18, 2000 Amend. p. 2)

In the March 11, 2000 Notice of Allowability, the Patent Examiner based the allowance of the '863 Patent claims on, *inter alia*, the particular pharmaceutically acceptable carrier having the claimed spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent.

> However the prior art does not show nor fairly suggest applicants composition comprised of galanthamine hydrobromide (1:1) and a particular pharmaceutically acceptable carrier. The particular combination of a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent and an insoluble or poorly soluble cross-linked polymer disintegrant enables the fast dissolution of the tablet.

C. The '527 Patent Claims and Specification

The '527 patent to Gilis et al. issued on May 19, 2002 and is assigned to Janssen Pharmaceutical N.V. The '527 Patent will expire on June 6, 2017.

The '527 patent has seven claims directed to a particular fast-dissolving galanthamine hydrobromide tablet and to methods of using galantamine hydrobromide tablets to treat various disorders, including dementia, Alzheimer's dementia, mania, and nicotine dependency. Each of the claims requires the tablet to have the same diluent comprising the spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as required by the '863 patent. Only claims 1 and 6 are independent:

> 1. A method of treating a disorder selected from dementia, mania or nicotine dependence in a patient in need thereof comprising administering to the patient a tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.
>
> 2. The method of claim 1 wherein the disorder is dementia.
>
> 3. The method of claim 2 wherein the disorder is Alzheimer's dementia.
>
> 4. The method of claim 1 wherein the disorder is mania.
>
> 5. The method of claim 1 wherein the disorder is nicotine dependence.
>
> 6. A fast-dissolving galanthamine hydrobromide (1:1) tablet made by (i) dry blending the active ingredient, an insoluble or poorly soluble cross-linked polymer disintegrant and an optional glidant with a diluent comprising a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25); (ii) optionally mixing a lubricant with the mixture obtained in step (i); (iii) compressing the mixture obtained in step (i) or in step (ii) in the dry state into a tablet; and (iv) optionally film-coating the tablet obtained in step (iii).

The specification of the '527 patent is virtually identical to the specification of the '863 patent.

D. The '527 Patent Prosecution History

The '527 Patent issued from U.S. Application No. 09/585,122, filed June 1, 2000, which is a continuation of U.S. Application No. 09/202,187, which issued as the '863 patent.

In a Preliminary Amendment, applicants cancelled the pending claims and added six new claims directed toward methods of treating various disorders, including dementia,

Alzheimer's dementia, mania or nicotine dependence and a galanthamine hydrobromide tablet made by a particular process. (June 1, 2000 Prel. Amend.) The Examiner objected to the dependent claim directed to method of treating nicotine dependence as being dependent upon a rejected base claim, but indicated the claim would be allowable if rewritten in independent form. (Dec. 6, 2000, OA) The remaining method claims were rejected under 35 U.S.C. § 102 as anticipated by U.S. Patent No. 4,663,318. *Id.* The Examiner rejected the tablet claim for obviousness-type double patenting in view of U.S. Patent No. 6,099,863. *Id.*

To overcome the § 102 rejection, the applicants argued that U.S. Patent No. 4,663,318 does not teach a pharmaceutically acceptable carrier that "comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant." (Mar. 7, 2001, Amend. p. 2). The applicants also offered to submit a terminal disclaimer to overcome the double patenting rejection. *Id.*

The next Office Action maintained the obviousness-type double patenting rejection of the tablet claim. The Examiner further rejected the tablet claim as not enabling any diluent or any disintegrant, but did state that the specification enabled a diluent comprised of a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) and an insoluble or poorly soluble cross-linked polymer disintegrant. (May 22, 2001 OA). The method claims were allowed. *Id.*

On August 22, 2001, the applicant amended the tablet claim by requiring "an insoluble or poorly soluble cross-linked polymer disintegrant and an optional glidant with a diluent comprising a spray-dried mixture of lactose monohydrate and a microcrystalline cellulose (75:25)" also be blended with the active ingredient and submitted a terminal disclaimer to overcome the double patentiug rejection of the tablet claim. (Aug. 22, 2001 Amend.) The Notice of Allowance was mailed September 13, 2001.

E. Alphapharm's Tablets Do Not Include a Diluent Comprised of a Spray-Dried Mixture of Lactose Monohydrate and Microcrystalline Cellulose and Thus Do Not Infringe the '863 or '527 Patent

Alphapharm's proposed tablets, as specified in its ANDA, do not contain a diluent comprised of a spray-dried mixture of 75% lactose monohydrate and 25% of microcrystalline cellulose and therefore do not infringe the '863 or the '527 patent claims. "Literal infringement requires that the accused device contain each limitation of the claim exactly; any deviation from the claim precludes a finding of literal infringement." *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1454 (Fed. Cir. 1998). In order to infringe either the '863 or '527 patent, an accused product must contain a diluent comprised of spray-dried mixture of lactose monohydrate and microcrystalline cellulose in a 75 to 25 ratio.

The stated objective in both the '863 and the '527 patents is to provide a self-dissolving galanthamine hydrobromide tablet in which there is at least 80% dissolution after 30 minutes and that "compliance with this dissolution specification is only met using a particular diluent containing disintegrant, and a second disintegrant." The particular diluent

is a spray-dried mixture of the diluent lactose monohydrate and the disintegrant microcrystalline cellulose in a 75:25 ratio. The '527 and '863 patents have thus delineated very specific ingredients in the diluent and ratios of those ingredients. These limitations are present in each independent claim, and thus in the every claim of the '527 and the '863 patents. *See Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1984).

Since lactose monohydrate is the sole diluent in Alphapharm's galantamine hydrobromide tablets, the tablets do not meet the claim limitations requiring a two part diluent having 75% lactose monohydrate and 25% microcrystalline cellulose as required by both the '863 and '527 patent. If even one limitation is not met as claimed, there is no literal infringement. *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998). As such, Alphapharm's product does not literally infringe either patent.

F. Alphapharm's Tablets Do Not Infringe the '527 or '863 Patents Under the Doctrine of Equivalents.

There is likewise no infringement under the doctrine of equivalents because the use of lactose monohydrate alone as a diluent cannot be viewed as the equivalent of the spray-dried mixture diluent in view of the '863 and '527 Patent applicant's statement such a formulation did not achieve the desired results.

Alphapharm's product also cannot infringe under the doctrine of equivalents because to do so would ignore the claim limitation requiring the diluent to be composed of two ingredients. *See Dolly*, 16 F.3d at 398 (stating a "court cannot convert a multilimitation claim to one with fewer limitations to support a finding of equivalency"). Additionally, in order to overcome § 112 rejection, claim 6 of the '527 patent was amended during prosecution to require the blending of a diluent comprising a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) As such, this narrowing amendment made for reasons of patentability gives rise to an estoppel preventing infringement under the doctrine of equivalents. Thus, for these additional reasons, there cannot be infringement under the doctrine of equivalents.

G. Alphapharm's Tablets Do Not Infringe Claims 4 and 5 of the '527 Patent

Claims 4 and 5 of the '527 patent are limited to methods of treating mania and nicotine dependence, respectively. Alphapharm's ANDA is directed to the treatment of Alzheimer's disease, not to the treatment of mania and/or nicotine dependence. Treating Alzheimer's Disease is not equivalent to treating mania or nicotine dependence. Thus, for this additional reason, claims 4 and 5 are also not infringed.

IV. THE '318 PATENT IS NOT INFRINGED, IS INVALID AND/OR UNENFORCEABLE

A. The '318 Patent Claims and Specification

U.S. Patent No. 4,663,318 ("the '318 patent") to Davis issued on May 5, 1987 and is currently assigned to Synaptech Inc. The '318 patent expires on December 14, 2008.

The '318 patent has seven claims directed to a method of treating Alzheimer's disease and related dementias by administering galantamine. Only claim 1 is independent. Each of the claims are recited below:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.
2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.
3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.
4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.
5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.
6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.
7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

The specification of the '318 patent contains only slightly more than one page of text. The patent admits that galanthamine and its salts are known to have anticholinesterase properties, that galanthamine has been administered to human patients, and that galanthamine has been used to improve memory in animal testing. (Col. 1, ll. 11-33). The patent includes ten lines describing an animal model for Alzheimer's disease in humans, but does not state if galanthamine was ever tested in this animal model. The patent does not set forth any completed experiments or any *in vitro* or *in vivo* testing of galanthamine of any kind.

B. The '318 Prosecution History

The '318 patent was filed on January 15, 1986, as U.S. Application No. 06/819,141. This application does not claim priority to any other application. In the first Office Action,

dated April 10, 1986, all of the claims were rejected under 35 U.S.C. § 112, ¶ 2 as being indefinite for reciting "diagnosing" in the claims and as obvious under 35 U.S.C. § 103 over two Chemical Abstract references. The Patent Examiner stated that the prior art references taught that galantamine hydrobromide possessed activity (i.e. improvement of memory) that would have value in treating the effects of Alzheimer's disease. (Apr. 10, 1986 OA, p. 3)

The September 9, 1986 amendment argued that little was known about the cause of Alzheimer's disease but "useful results have been reported in some cases by treatment with physostigmine but because of its poor therapeutic index, widespread use is not likely to occur and there is therefore no generally effective treatment available". The '318 Patent applicant then referred to a prior art publication to show what an effective Alzheimer's treating drug would require:

> The theoretical possibility of developing a long acting preparation from an agent with good brain penetration and possibly some selectivity of action towards the relevant cortical cholinergic system must be seen as a major challenge for researchers working on Alzheimer's disease.
> (Sept. 9, 1986 Amend. p. 2)

The applicant stated that she "currently has experiments underway using animal models which are expected to show that treatment with galanthamine does result in an improvement in the condition of those suffering from Alzheimer's disease. It is expected that data from this experimental work will be submitted to the Examiner promptly thereafter." *Id.* No experiments were submitted to the PTO.

To overcome the art rejection, the applicant argued that it is a "non-sequitur" that since galanthamine has an effect on improving short-term memory and on restoring memory after it has been destroyed, that it would be useful in treating Alzheimer's disease. *Id.* at p. 3. The applicant stated that memory loss is involved with Alzheimer's disease is apparently associated with physiological changes in the brain and that there "is no way of predicting that because a chemical may have an effect on memory in a normal brain (which is what is indicated in the cited references) it would have any effect on a brain that has suffered such physiological changes." *Id.* at pp. 3-4. The applicant further said that the teaching of the Chaplygina Chemical Abstract that "galanthamine reverses the amnesia-producing effects of scopolamine" would be expected of an anticholinesterase and that "[n]othing in this teaching leads to an expectation of utility against Alzheimer's disease. There are many anticholinesterase drugs available" but Alzheimer's disease is still regarded as untreatable. Id. at p. 6.

The applicant stated that of 39 possible compounds it found in the literature to facilitate memory in studies of animals and humans without brain lesions, ten were tested for the treatment of Alzheimer's disease and only physostigmine was effective in treating Alzheimer's disease. The applicant admitted that galanthamine and its properties have been known for years, but argued that no one suggested that it should be used to treat Alzheimer's disease. The claims were allowed on October 20, 1986.

C. The '318 Patent Is Invalid over Prior Art

Prior to the filing of the patents at issue, the disruption of the cholinergic system was implicated as a major factor in cognitive impairment associated with Alzheimer's disease. This was reported as the "cholinergic hypothesis." *See, e.g.*, Johns, C.A., *The Cholinergic Treatment Strategy in Aging and Senile Dementia*, Psychopharmacology Bulletin, Vol. 19, No. 2, pp. 185-197 (1983). One cholinergic treatment strategy of Alzheimer's disease was to increase the available acetylcholine by limiting its breakdown, such as through the administration of acetylcholinesterase inhibitors. *See id.* at 192, 193 (stating "acetylcholinesterase inhibitors show more promise as a treatment strategy" in Alzheimer's dementia and that "trials of pharmacologic agents that enhance cholinergic activity should be aggressively pursued, as they offer a rational treatment strategy"). Numerous other references also suggested the use of anticholinesterase inhibitors to treat Alzheimer's dementia. *See, e.g.*, Kendall, M.J. et al., *Therapeutic Progress-Review XVIII Alzheimer's Disease*, J. Clin. & Hosp. Pharm. (1985) 10:327-336; Thal, L.J., et al., *Memory Enhancement with Oral Physostigmine in Alzheimer's Disease*, N. Engl. J. Med. March 24, 1983, p. 720 ("Such drugs, which are potent and specific enhancers of the cholinergic system, may prove to be clinically useful in the treatment of Alzheimer's disease."); Comfort, A., *Cholinesterase Inhibition in Treatment of Alzheimer's Dementia,*" Lancet , Mar. 25, 1978, pp. 659-660.

Also prior to the filing of the patents at issue, two anticholinesterase inhibitors, physostigmine and tacrine, were used to treat Alzheimer's disease. *See, e.g.*, K.L. Davis, et al., *Enhancement of Memory by Physostigmine*, N. Engl. J. Med. 1979; 301:946 (reporting parenteral physostigmine improved memory in patients with Alzheimer's disease); Thal, L.J., et al., *Memory Enhancement with Oral Physostigmine in Alzheimer's Disease*, N. Engl. J. Med. March 24, 1983, p. 720; Summers W.K., *"Oral Tetrahydroaminoacridine in Long-Term Treatment of Senile Dementia, Alzheimer's Type,"* N. Engl. J. Med. Nov. 13, 1986, pp. 1241-1245; U.S. Patent No. 4,631,286 (directed to tacrine derivatives and showing tacrine as a prior art compound with Alzheimer's disease treating activity).

Additionally, it was known that the pharmacologic blockade of cholinergic function, such as with scopolamine, produced memory deficits similar to those seen in Alzheimer's disease. Greenwald, B.S., *Experimental Pharmacology of Alzheimer's Disease*, The Dementias, (1983) pp. 87-102. Treatment of the symptoms of Parkinson's disease through the replacement of the associated deficit of dopamine with levodopa prompted researchers to hope that similar success in the treatment of Alzheimer's dementia could be attained by enhancing cholinergic function. *See, e.g.*, Comfort, A., *Cholinesterase Inhibition in Treatment of Alzheimer's Dementia*" Lancet , Mar. 25, 1978, pp. 659-660.

The art provided motivation to try other anticholinesterase inhibitors to treat Alzheimer's dementia. For example, Lancet reported that an "obvious line of attack [to treat Alzheimer's dementia] would be the use of anticholinesterase. Unfortunately none of the anticholinesterase drugs available for other therapeutic purposes look safe enough for trial, and all of them act systemically. What is needed is a cholinesterase inhibitor with predominantly central effects." A. Comfort, *Cholinesterase Inhibition in Treatment of Alzheimer's Dementia*, Lancet, Mar. 25, 1978, pp. 659.

Prior to the filing of the patents at issue, galantamine was a known cholinesterase inhibitor that crossed the blood brain barrier and prevented the breakdown of acetylcholine in the cholinergic system. *See, e.g.,* Heinrich, M. et al., *Galanthamine from Snowdrop - the Development of a Modern Drug against Alzheimer's Disease from Local Caucasian Knowledge*, J. Enthnopharmacology, 92 (2002) 14-162. Galantamine has been commercially available under the name Nivalin since 1958 in an injection form and since 1984 in a tablet form. Nivalin (galantamine) has been used in the treatment poliomyelitis, facial neuralgia, stammering, infantile cerebral lesions, and asphasic syndromes. *Id.;* Daskalov, D. et al., *Nivalin, Application in Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes*, Medico Biologic Info (1980), pp. 9-11; U.S. Patent No. 6,358,527 (col. 1, ll. 37-45).

Thus, prior to the effective date of the '318 Patent it was known that cholinesterase inhibitors would be useful for the treatment of Alzheimer's disease and that the cholinesterase inhibiting compounds physostigmine and tacrine were known to possess properties effective for the treatment of Alzheimer's disease. The confirmation that galantamine with properties similar to physostigmine and tacrine would be effective for the treatment of Alzheimer's disease was routine and not unexpected. Thus, claim 1 of the '318 Patent employing galantamine for the treatment of Alzheimer's disease is invalid because the same was obvious to one of ordinary skill in the art over the prior art use of physostigmine and tacrine for the same purpose, the suggestion to try additional centrally acting acetylcholinesterase inhibitors, and the therapeutic use of galantamine to treat other indications.

The dependent claims contain dosing or administration limitations. Claims 2 and 3 require daily parental administration of 5-1000 mg and 50-300 mg of galanthamine, respectively. Claims 4 and 5 require daily oral administration of 10-2000 mg and 100-600 mg, respectively. Claim 6 requires parental administration of galanthamine at a dosing rate of 0.1 to 4 mg/kg body weight of a patient. Claim 7 requires intracerebroventricular administration via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg. These limitations are merely dosing ranges that do not render the claims patentable.

Although secondary considerations of patentability such as commercial success must be given due consideration to assess the validity of a claim under 35 U.S.C. § 103, the claimed subject matter of the '318 patent is obvious. There is insufficient evidence of secondary considerations presented during the prosecution history of the '318 Patent, to validate an otherwise invalid claims. Any such secondary considerations are insufficient to overcome the strong showing of obviousness.

D. Alphapharm's Proposed Product Does Not Infringe Claims 2, 3, 5, 6 or 7 of the '318 Patent

Alphapharm's Proposed Product contains galantamine in 4 mg, 8 mg and 12 mg tablets in which the daily dosage proposed is the same as that for the branded galantamine hydrobromide, namely 6-32 mg/day with the recommended dosage being 16-24 mg/day.

Claims 3 and 5 each require a dosage well above the dosage range anticipated for the Proposed Alphapharm Product. Accordingly, there is no infringement of claims 3 and 5.

Claims 2, 6 and 7 require administration by a method different than the oral method of administration intended for use with the Proposed Alphapharm Product. In particular, claims 2 and 6 require parental administration while claim 7 requires intracerebroventricular administration through an implanted reservoir. Accordingly, claims 2, 6 and 7 are not infringed by the Proposed Alphapharm Product.

CONCLUSION

The marketing of Alphapharm's proposed galantamine hydrobromide tablets in the United States will not infringe any valid and enforceable claim of the '318, '527 or '863 patents.

In addition to the factual and legal bases set forth here, Alphapharm expressly reserves the right to develop, make and assert further arguments and defenses relating to noninfringement, invalidity and/or unenforceability of this patent as the record develops.

OFFER OF CONFIDENTIAL ACCESS AND CONFIDENTIALITY AGREEMENT PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

THIS OFFER OF CONFIDENTIAL ACCESS AND CONFIDENTIALITY AGREEMENT ("Agreement") by and between ALPHAPHARM PTY. LTD., ("Alphapharm" or the "Offeror"), and JANSSEN PHARMACEUTICA PRODUCTS, L.P., JANSEEN PHARMACEUTICA NV, and/or SYNAPTECH INC. (collectively the "Offerees") is made effective upon a request by an Offeree for access to Alphapharm's Abbreviated New Drug Application for galantamine hydrobromide tablets, 4 mg, 8 mg and 12 mg ("Alphapharm's ANDA").

W I T N E S S E T H :

WHEREAS, in accordance with § 505(j)(5)(C)(i)(III) of the Federal Food, Drug and Cosmetic Act ("the Act") as amended by Title XI of the Medicare Prescription Drug, Improvement and Modernization Act of 2003, Alphapharm offers to make certain "Information" (as defined below) concerning its ANDA available to Janssen subject to the terms and conditions of this Agreement;

NOW, THEREFORE, in consideration of the foregoing premises and the furnishing of Information by Alphapharm, the receipt and sufficiency of which is hereby acknowledged, and intending to be legally bound hereby, the parties agree as follows:

1. DEFINITIONS

(a) "Information" means any and all information that the Providing Party (as hereafter defined) or its representatives provides or furnishes to the Receiving Party (as hereafter defined) or its representatives, regardless of whether: (i) such Information is specifically marked

By: _____

Name: _____

Title: _____

Date: _____

JANSSEN PHARMACEUTICA N.V.

By: _____

Name: _____

Title: _____

Date: _____

SYNAPTECH INC.

OFFER OF CONFIDENTIAL ACCESS AND CONFIDENTIALITY AGREEMENT PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

THIS OFFER OF CONFIDENTIAL ACCESS AND CONFIDENTIALITY AGREEMENT ("Agreement") by and between ALPHAPHARM PTY. LTD., ("Alphapharm" or the "Offeror"), and JANSSEN PHARMACEUTICA PRODUCTS, L.P., JANSEEN PHARMACEUTICA NV, and/or SYNAPTECH INC. (collectively the "Offerees") is made effective upon a request by an Offeree for access to Alphapharm's Abbreviated New Drug Application for galantamine hydrobromide tablets, 4 mg, 8 mg and 12 mg ("Alphapharm's ANDA").

W I T N E S S E T H :

WHEREAS, in accordance with § 505(j)(5)(C)(i)(III) of the Federal Food, Drug and Cosmetic Act ("the Act") as amended by Title XI of the Medicare Prescription Drug, Improvement and Modernization Act of 2003, Alphapharm offers to make certain "Information" (as defined below) concerning its ANDA available to Janssen subject to the terms and conditions of this Agreement;

NOW, THEREFORE, in consideration of the foregoing premises and the furnishing of Information by Alphapharm, the receipt and sufficiency of which is hereby acknowledged, and intending to be legally bound hereby, the parties agree as follows:

1. DEFINITIONS

(a) "Information" means any and all information that the Providing Party (as hereafter defined) or its representatives provides or furnishes to the Receiving Party (as hereafter defined) or its representatives, regardless of whether: (i) such Information is specifically marked

or designated as "confidential" or "proprietary", (ii) such Information is patentable, copyrightable or otherwise protected by law, or (iii) such Information is furnished verbally, in writing or in electronic form. "Information" includes, but is not limited to, any and all notes, memoranda, analyses, compilations, studies or other documents (whether in hard copy or electronic media) prepared by either party which contain or otherwise reflect such Information, and any and all copies, extracts or other reproductions of any of the same.

(b) Notwithstanding the foregoing, the term "Information" does not include information that: (i) is or becomes available to the public through no wrongful act of the Receiving Party or its representatives; (ii) is known to the Receiving Party on the date of this Agreement, as evidenced by written records of the Receiving Party existing on said date; (iii) is received from a third party who has the right to disclose the same to the Receiving Party; (iv) is in the rightful possession of the Receiving Party free of any obligation of confidentiality; or (v) is independently developed by the Receiving Party without reference to, or misuse of, information furnished by the Providing Party.

(c) "Providing Party" means the party furnishing Information, and includes its subsidiary and affiliated corporations.

(d) "Receiving Party" means the party receiving Information, and includes its subsidiary and affiliated corporations.

(e) "Representatives" means any party's employees, agents or other representatives, including advisors, attorneys, accountants, financial advisors and potential financing sources.

2. **CONFIDENTIALITY**

(a) The parties are authorized to provide Information to each other for the sole and limited purpose of evaluating possible infringement of the patents that are the subject of Alphapharm's certification pursuant to § 505(j)(2)(A)(vii)(IV) in connection with its ANDA (U.S. Patent No. 4,663,318 ("the '318 patent"); U.S. Patent No. 6,099,863 ("the '863 patent"); and U.S. Patent No. 6,358,527 ("the '527 patent")(collectively, "the Listed Patents").

(b) Persons entitled to access to the Information on the part of Receiving Party are restricted to (i) outside counsel engaged or employed by the Receiving Party to represent them and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that such outside counsel has been identified to the Providing Party in writing, (ii) no more than 2 in-house counsel and (iii) independent consultants and experts assisting in the evaluation of the Information for the Receiving Party and any employees and assistants under the control of such consultant or expert.

(c) Persons with access to the Information shall: (i) shall be identified to the Providing Party before Information is provided under this Agreement; (ii) shall keep Information furnished to them by the Providing Party strictly confidential and not disclose it to unauthorized employees or agents of the Receiving Party; (iii) take all reasonable precautions to safeguard such Information against unauthorized disclosure; and (iv) shall not take any action inconsistent with the Providing Party's ownership of such Information.

(d) Except to the extent required by law or judicial process and in accordance with paragraph 4 below, the Receiving Party shall not disclose to any third person or entity other than those provided for in paragraph 2(b): (i) the Providing Party's Information, (ii) the fact that such

Information was disclosed to the Receiving Party, or (iii) the fact that an evaluation is taking place with respect to the Information, including the status thereof, unless exempted from one or more of these prohibitions by the express prior written consent or authorization of the Providing Party.

(e) The Receiving Party shall not copy, reproduce, or reduce to writing any part of the Information furnished to it by the Providing Party except as is reasonably necessary to accomplish the purpose of the Agreement. Any such copies, reproductions or reductions to writing shall become the property of the Providing Party.

(f) The Receiving Party shall be responsible for any breach of this Agreement by its officers, directors, employees or other representatives, and shall take all reasonable measures to restrain such persons from the unauthorized use or disclosure of the Information.

3. USE OF INFORMATION

The Receiving Party shall use the Information solely for the limited purpose of evaluating Alphapharm's possible infringement of the Listed Patents and for no other purpose.

4. GOVERNMENTAL REQUESTS FOR DISCLOSURE

In the event that the Receiving Party or any of its Representatives receives a request or is required by applicable law to disclose to a court or government agency of competent jurisdiction all or any part of the Providing Party's Information, the Receiving Party or its representatives shall promptly notify the Providing Party of the request, and shall to the extent requested, consult with and assist the Providing Party in seeking a protective order or other appropriate protective remedy. If such order or other remedy is not obtained or the Providing Party waives compliance with the terms hereof, the Receiving Party or its representatives, as the case may be, shall

disclose only that portion of the Information which, in the reasonable opinion of its counsel, is legally required to be disclosed, and shall exercise their respective best efforts to assure that confidential treatment will be accorded such Information by the persons or entities receiving it. The Providing Party shall be given a reasonable opportunity to review the Information prior to its disclosure.

5. NO REPRESENTATION, COMMITMENT, LICENSE OR WAIVER

(a) The Providing Party makes no representation or warranty of any kind, whether express or implied, about the accuracy or completeness of the Information. Neither the Providing Party, nor any of its officers, directors, shareholders, employees or representatives shall have any liability to the Receiving Party or to any other person or entity resulting from use of the Information.

(b) No failure or delay by the Providing Party in exercising any right, power or privilege hereunder shall operate as a waiver thereof.

6. RETURN OF INFORMATION

(a) If the Receiving Party does not file suit against Alphapharm alleging infringement of the Listed Patents within forty-five (45) days of receipt of the Notice and Detailed Statements (the "45-day periods") which this offer accompanies, the Receiving Party shall cause persons entitled to access to the Information thirty (30) days after the expiration of the 45-day period, to destroy or return to Alphapharm the portions of the ANDA provided and all notes, analyses, studies or other documents to the extent that they contain information in the ANDA, and the Receiving Party shall notify Alphapharm that this has been done.

(b) If the Receiving Party files suit against Alphapharm alleging infringement of the Listed Patents within the 45-day periods:

(1) while the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents to the extent that they contain information in the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Alphapharm. Until such a protective order is entered, subsection (2)(c)(ii) above continues to apply;

(2) Receiving Party shall cause persons entitled to access to the Information to destroy or return to Alphapharm the portions of the ANDA provided and all notes, analyses, studies or other documents prepared to the extent that they contain information in the ANDA, within thirty (30) days after the final determination of the action brought against Alphapharm.

7. INJUNCTIVE RELIEF

The parties agree that money damages will not be a sufficient remedy for any breach of this Agreement by the Receiving Party or its representatives, and that the Providing Party is entitled to injunctive relief and specific performance as remedies for any such breach. Such remedies shall not be deemed to be the exclusive remedies for a breach of this Agreement but shall be in addition to all other remedies available at law or in equity.

8. TERM; TERMINATION

This Agreement shall be effective upon execution of this Agreement by Alphapharm and Janssen for providing access to Alphapharm's ANDA, and shall remain in effect until such time as the Information is returned or destroyed pursuant to Paragraph 6 above. The Agreement may be renewed upon such terms as may be agreed upon by the parties. Upon termination of this

Agreement, the Receiving Party shall fulfill its obligations to return the Providing Party's Information pursuant to above paragraph 6 of this Agreement. The Receiving Party's obligations of confidentiality pursuant to above paragraph 2 shall survive the termination of this Agreement.

9. SEVERABILITY

The invalidity or unenforceability of any provision of this Agreement shall not affect the validity or enforceability of any other provision, all of which shall remain in full force and effect.

10. ASSIGNMENT

This Agreement shall not be assigned without the prior written consent of the Providing Party.

11. GOVERNING LAW

This Agreement shall be construed in accordance with the laws of the State of New York, without regard to conflict of laws principles.

12. HEADINGS

The section headings in this Agreement are for convenience only, and shall not alter or affect the meaning or interpretation of any provision of this Agreement.

13. COUNTERPARTS

This Agreement may be executed in one or more counterparts, all of which shall be considered one and the same Agreement.

14. COMMUNICATIONS

Delivery of any counterpart signature page of this Agreement, written communication or notice hereunder by facsimile shall be equally as effective as delivery of a manually executed original of such counterpart signature page, communication or notice. Any party delivering a counterpart signature page, written communication or notice hereunder by facsimile shall also deliver a confirmatory hand-signed original.

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed upon a request by an Offeree for access to Alphapharm's ANDA.

By: _____

Name: _____

Title: _____

Date: _____

ALPHAPHARM PTY. LTD.

By: _____

Name: _____

Title: _____

Date: _____

JANSSEN PHARMACEUTICAL PRODUCTS, L.P.

CERTIFICATE OF SERVICE

I hereby certify that on the 21st day of February, 2006, the attached **NOTICE OF DEPOSITION UNDER FED. R. CIV. P. 30(b)(6) TO ALPHAPHARM PTY LTD.** was served upon the below-named counsel of record at the address and in the manner indicated:

John W. Shaw, Esquire — HAND DELIVERY
Young Conaway Stargatt & Taylor, LLP
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, DE 19801

Daniel F. Attridge, P.C. — VIA FEDERAL EXPRESS
Kirkland & Ellis LLP
655 15th Street, N.W.
Washington, DC 20005-5793

Mary B. Matterer, Esquire — HAND DELIVERY
Morris James Hitchens & Williams LLP
222 Delaware Avenue, 10th Floor
Wilmington, DE 19801

William A. Rakoczy, Esquire — VIA FEDERAL EXPRESS
Rakoczy Molino Mazzochi Siwik LLP
6 West Hubbard Street, Suite 500
Chicago, IL 60601

Richard L. Horwitz, Esquire — HAND DELIVERY
Potter Anderson & Corroon LLP
Hercules Plaza, 6th Floor
1313 N. Market Street
P.O. Box 951
Wilmington, DE 19899

Stuart D. Sender, Esquire — VIA FEDERAL EXPRESS
Budd Larner, P.C.
150 John F. Kennedy Parkway
Short Hills, NJ 07078

John C. Phillips, Jr., Esquire — HAND DELIVERY
Phillips, Goldman & Spence, P.A.
1200 North Broom Street
Wilmington, DE 19806

Lynn M. Ulrich, Esquire — VIA FEDERAL EXPRESS
Winston & Strawn LLP
35 West Wacker Drive
Chicago, IL 60601

Richard D. Kirk, Esquire — HAND DELIVERY
The Bayard Firm
222 Delaware Avenue, Suite 900
Wilmington, DE 19899

Robert J. Gunther, Jr., Esquire — VIA FEDERAL EXPRESS
Latham & Watkins LLP
885 Third Avenue, Suite 1000
New York, NY 10022-4802

Frederick L. Cottrell, III, Esquire — HAND DELIVERY
Richards, Layton & Finger
One Rodney Square
Wilmington, DE 19801

Alan H. Bernstein, Esquire — VIA FEDERAL EXPRESS
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street, 12th Floor
Philadelphia, PA 19103

Philip A. Rovner, Esquire — HAND DELIVERY
Potter Anderson & Corroon LLP
Hercules Plaza
Wilmington, DE 19801

Barbara S. Wahl, Esquire — VIA FEDERAL EXPRESS
Arent Fox PLLC
1050 Connecticut Avenue, N.W.
Washington, DC 20036-5339

/s/ Lauren E. Maguire

Lauren E. Maguire